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Extracellular Spike Detection from Multiple Electrode Array using Novel Intelligent Filter and Ensemble Fuzzy Decision Making

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Abstract

Background

The information obtained from signal recorded with extracellular electrodes is essential in many research fields with scientific and clinical applications. These signals are usually considered as a point process and a spike detection method is needed to estimate the time instants of action potentials. In order to do so, several steps are taken but they all depend on the results of the first step, which filters the signals. To alleviate the effect of noise, selecting the filter parameters is very time-consuming. In addition, spike detection algorithms are signal dependent and their performance varies significantly when the data change.

New Methods

We propose two approaches to tackle the two problems above. We employ ensemble empirical mode decomposition (EEMD), which does not require parameter selection, and a novel approach to choose the filter parameters automatically. Then, to boost the efficiency of each of the existing methods, the Hilbert transform is employed as a pre-processing step. To tackle the second problem, two novel approaches, which use the fuzzy and probability theories to combine a number of spike detectors, are employed to achieve higher performance.

Results, Comparison with Existing Method(s) and Conclusions

The simulation results for realistic synthetic and real neuronal data reveal the improvement of the proposed spike detection techniques over state-of-the art approaches. We expect these improve subsequent steps like spike sorting.

Keywords: Extracellular spike detection, evolutionary algorithms, Hilbert transform, fuzzy and probability theory, ensemble empirical mode decomposition.

1. Introduction

Multiple electrode array (MEA) is a usual tool in neuroscience that records simultaneous activity of several neurons in a piece of neural tissue. The electrode may be intracellular, although it is more commonly extracellular. The recorded signals are small, and they frequently arise from electrical activity in some nearby neurons [1,2].

The majority of techniques for the analysis of neural activity begin with spike detection to identify the time instants at which action potentials occurred from one or several neurons. The quality of the spike detection algorithm notably influences the performance of the subsequent steps, such as spike sorting (grouping the recorded spikes into clusters based on the similarity of their shapes). Errors in detecting the number and location of spikes will inevitably propagate through all later analyses [1, 3, 4].

There are a number of reasons that make the spike detection a challenging task. First, extracellularly recorded spike trains are unavoidably corrupted by the superimposed activity of multiple neurons and the noise from the recording hardware. Second, implanted microelectrodes usually pick up the concurrent electrical activities with various sizes and shapes from an unknown number of local neurons. Third, the activity of distant neurons may emerge as noise that is highly correlated with the useful signal [4, 5].

Few decades ago, spike detection was being performed by using simple amplitude thresholds. This method detects events, like spikes, by considering a peak that is higher than a threshold defined by a user or a statistical property of a signal, such as mean, standard deviation, or median. The threshold can been selected manually by visual inspection or automatically. Although this kind of spike detection method is appropriate for intracellular recordings, extracellular recordings from high-density MEAs and low-impedance microelectrodes frequently have low signal-to-noise ratio (SNR), and the problem becomes far more complex [6, 7].

Another widespread method to detect spikes is based on template matching, a technique used in signal and image processing. In this method, templates representing a typical waveform are utilized as benchmarks. The initial stage of this method is to select a waveform that represents a typical spike shape as template. In the second stage, the method locates possible events in the signal that "closely resemble" the template. Finally, there is a thresholding stage. Early template matching methods often started with the experimenter identifying a couple of high-quality spikes, and using them to train a filter. However, this is unfeasible, especially when there are a large number of electrodes [1, 6, 8]. Even though the template matching algorithm often detects spike events better than simple threshold algorithms, its performance depends on a priori knowledge of the spike shape to create the template. In addition, since the automatic selection of a template in a noisy neuronal data is very complicated, the performance of the method decreases in poor SNRs [1, 6, 8].

In [5], an automatic spike detection method based on piecewise optimal morphological filter is suggested. The interesting benefit of this method is that the piecewise optimal morphological filter can highlight the spikes categorized by their structural elements and successfully reduce the background noise. However, the method missed spike events with dissimilar morphological characters from most of spike events presented in data window. This increased the false detection rate of the algorithm notably. This problem was, at least partially, due to the fact that the burst of one or two types of spikes makes the rest type of spikes uncommon within the data window, which leads to the bias of optimal structuring elements to bursting spikes.

A model-based algorithm to detect the spikes by taking into account the distributions of spike amplitudes, widths and frequencies was suggested in [9]. Quiroga showed that spike shapes can be distorted significantly by the causal filters frequently used for online spike detection. He illustrated this impact using elliptic filters, but similar results were obtained with Butterworth or Chebyshev causal filters [10].

There are also a number of approaches based on wavelet transform to detect the spikes in neuronal data [4, 11]. In [11], a spike detection method using discrete Haar transformation, which does not need a priori assumptions about spike shape or timing, was proposed. However, the approach assumed white noise and required an unnecessary inverse transformation from wavelet domain to time domain [4]. To overcome this problem, Nenadic and Burdick combined wavelet transforms with basic detection theory to enhance an unsupervised method for detecting spikes in extracellular neural recordings robustly [4]. The most important advantage of this approach is its ability to separate signals from noise by thresholding the wavelet coefficients and, therefore, this method performs well even in poor SNR. However, its main disadvantage is the need to assume a single spike shape resulting in the wavelet choice that is suboptimal for other spikes [8].

Another well-known approach uses signal transformations such as nonlinear energy operator (NEO or NLEO). This is a powerful tool for spike detection. However, when the signal contains multiple frequencies or components, the output of the method includes a DC part and a time-varying part, called cross-terms. The cross-terms and the presence of noise reduce the accuracy of this spike detection algorithm [1, 6, 8]. To overcome these problems, Azami and Sanei employed the smoothed NEO (SNEO) and some filters to detect the spikes in noisy neuronal data [1].

Mtetwa and Smith have presented five spike detection algorithms and three thresholding criteria for spike detection [12]. Among them, the best method was based on normalized cumulative energy difference (NCED). This method, inspired by the fact that the energy in a spike (either positive or negative) should be greater than that in noise of the same length, can be followed by multi-template-based spike sorting.

In [1], three new methods to detect the neuronal spikes buried in noise and interferences based on SNEO, fractal dimension (FD) and standard deviation were proposed. In order to overcome the impact of noise and to overcome the low speed of discrete wavelet transform (DWT), singular spectrum analysis (SSA), Kalman filter (KF) and Savitzky-Golay filter were used as pre-processing steps. In addition, since DWT, SSA, KF and Savitzky-Golay filter have several tunable parameters, Azami and Sanei proposed to use the residual signal obtained by empirical mode decomposition (EMD) as a filtered signal [1].

To sum up, there are still two outstanding problems in spike detection: 1) Usually, choosing appropriate parameters for each noise reduction method is a time-consuming task and needs to be done in many trials. 2) Generally, each spike detection approach is only suitable for a limited number of signal types and applications.

In order to overcome the first problem, we now propose an intelligent approach to set appropriate filter parameters automatically by two powerful evolutionary algorithms, namely genetic algorithm (GA) and new particle swarm optimization (NPSO). In addition, we suggest using an ensemble EMD (EEMD) method as a pre-processing noise reduction step. EEMD is a powerful new algorithm to decompose a complex time series into a number of intrinsic mode functions (IMFs) and a residual signal and it achieves better performance than EMD [13]. After using an intelligent filter or an EEMD to increase the accuracy of the existing methods, we propose to employ the Hilbert transform [14].

In order to tackle the second problem and achieve much better performance compared with those of the conventional neuronal data spike detection methods, we also propose two approaches based on the probability and fuzzy concepts that combine some existing approaches.

In the following section, the proposed intelligent filter and two methods to combine the existing algorithms are explained. Section 3 provides describes the dataset employed in this paper. Then, the results of the proposed methods and the conventional ones are compared. The conclusions of the paper are stated in the last section.

2. Proposed Methods

First, we explain a novel approach for selecting parameters automatically as well as introducing EEMD briefly. Then, the importance of using Hilbert transform for this application is described.

Finally, two novel methods for extracellular spike detection based on the fuzzy and probability concepts are defined in detail.

2.1. Noise reduction Methods

In this subsection, we discuss an intelligent filtering approaches and EEMD.

2.1.1. Intelligent approach for filtering

Here, we explain an approach to filter a signal. First, we introduce the SSA briefly and then propose an approach to enhance it. Next, after describing the Savitzky-Golay filter [1], we suggest an approach to improve it by the NPSO.

2.1.1.1. Improved Singular Spectrum Analysis by Genetic Algorithm

SSA, which is a flexible and powerful filtering tool suitable for many different types of signals, uses a subspace selection and reconstruction to make a desired signal [15, 16]. It is much faster than many existing filters such as those based on DWT and has been used for spike detection recently [1]. However, this process, like almost all filters, has an important short-coming, i.e. there are some parameters to be adjusted using a large number of trials. Sometimes, the range or average of the SNR is known or estimated. In this case, we propose a new method based on the GA. GA is a powerful search algorithm to find the approximate solutions in the defined space [17].

As a means of illustration, assume a Gaussian noise with SNR=2 dB is added to $x_1 = 5\sin(3\pi t)$. There are many ways for choosing the two parameters of SSA, i.e. window length (i.e. embedding dimension), l and m disjoint subsets $I = [I_1,...,I_m]$ to reconstruct the time series. The filtering process for a particular signal is sensitive to selection of these parameters. When l and I are selected too large, some important information of the original signal is removed by this filter. For too small I and l, however, this filter cannot attenuate destructive noises sufficiently. Moreover, in many applications due to lack of information about a signal, selecting these parameters is very difficult. To overcome this problem, in this study, we propose to use the GA with the following fitness function:

$$H = \left|SNR - \overline{SNR}\right| = \left|10.\log_{10}\left(\sum_{i=1}^{n}(x_f(i))^2 / \sum_{i=1}^{n}(x(i) - x_f(i))^2\right) - \overline{SNR}\right| \tag{1}$$

where n, x, x_f, and $\overline{SNR}$ are length of the signal, noisy signal, filtered signal, and SNR average of the original signal, respectively. $x - x_f$ is the noise. In other words, the GA tries to reduce H by changing l and I for the SSA. It should be mentioned that we use the proposed improved filter where the SNR average or at least the range of noise power is known. The GA employed here has 20 populations and the number of iterations is 30.

The results for three different sets of l and I are shown in Figure 1. As can be seen in Figure 1.a, l=6 and I=[1], where [k] states that only k eigentriples are used, are not large enough for filtering the signal with an SNR=2 dB. In Figure 1.b, l=30 and I=[1] and in Figure 1.c l=30 and I=[2] are chosen. It is evident that in both figures the amplitudes decrease considerably for an original signal with amplitude 5. Figures 1.b and 1.c demonstrate irregularities in the first and the last time samples. Here, GA is used to select suitable sets of filter parameters for SNR=2 dB. The result of employing the proposed filter is shown in Figure 2.c.

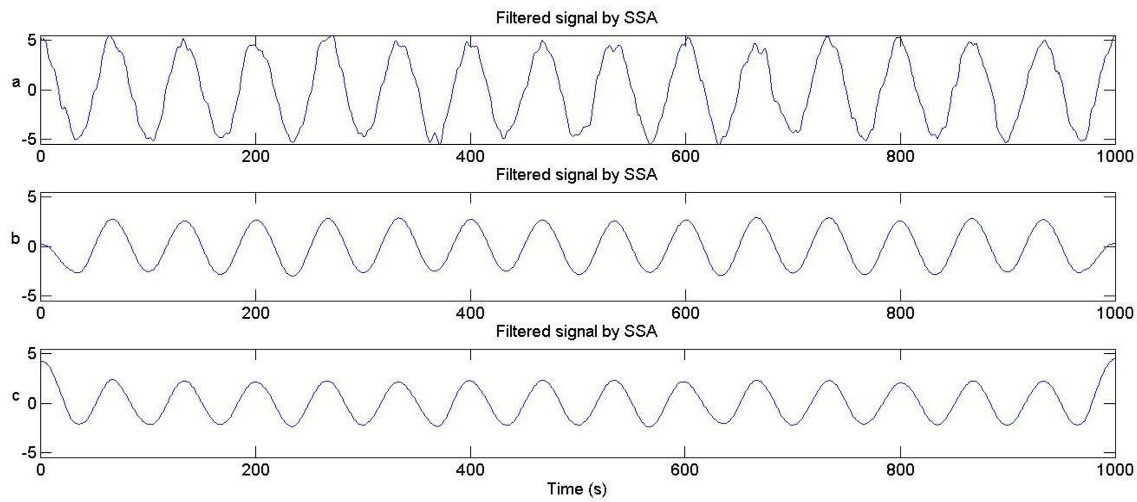

Figure 1. Results of applying three different sets of l and I for the SSA; (a) l=6 and I=[1], (b) l=30 and I=[1], and (c) l=30 and I=[2].

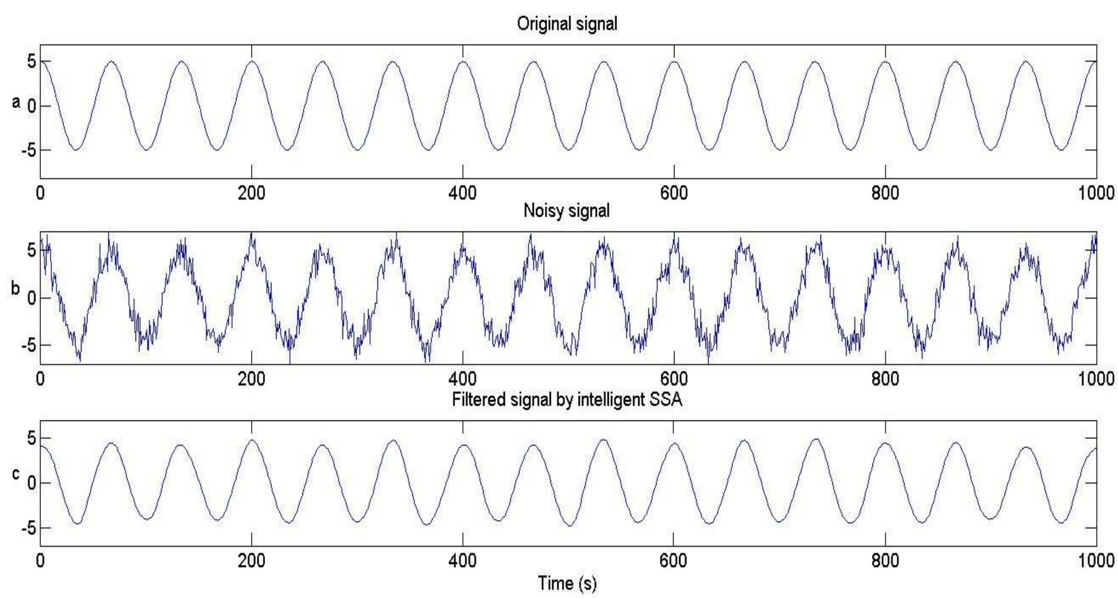

Figure 2. Improved SSA by GA; (a) original signal, (b) noisy signal (SNR=2 dB), and (c) optimal filtered signal.

2.1.1.2. Improved Savitzky-Golay Filter by New Particle Swarm Optimization

The idea of using computational methods to estimate an optimal set of parameters to filter the signals can be generalized for every kind of filter. For example, a powerful, fast, and flexible filter widely used in biomedical signal processing is the Savitzky-Golay filter [18, 19].

The coefficients of a Savitzky-Golay filter, when applied to a signal, perform a polynomial fitting P of the degree K to $N = N_r + N_l + 1$ points of the signal, where N is the window size and N_r and N_l are signal points in the right and left of a current signal point, respectively. One of the best important advantages of this filter is that it tends to keep the distribution extreme points, which are often flattened by other smoothing techniques [18,19]. This makes the Savitzky-Golay filter a favorable tool to detect the spikes. However, this filter has the aforementioned short-coming of requiring the adjustment of some parameters using a large number of trials. When N and K are selected too large, some important information of the original signal is removed by this filter. For too small N and K, however, this filter cannot attenuate destructive noises sufficiently.

Moreover, in many applications, due to the lack of information about the best polynomial order to fit a signal, selecting K is very difficult. To overcome this problem, in this study, we propose to use NPSO as a powerful and fast evolutionary algorithm [20] with a fitness function the same as Equation (1).

This is again illustrated using a similar setting to that of SSA. Assume a Gaussian noise with SNR=5 dB is added to $x_2 = \sin(5\pi t)$. The results for three different sets of K and N are shown in Figure 3. As can be seen in Figure 3.a, K=3 and N=19 are not large enough for filtering the signal with an SNR=5 dB. In Figure 3.b, K=5 and N=31, and in Figure 3.c K=3 and N=61 are chosen. It is evident that in both figures the amplitudes decrease considerably for an original signal with amplitude 1. Figure 3.b shows abnormalities in about 280 and 770 samples and Figure 3.c demonstrates irregularities in the first and the last time samples. Here, NPSO is used to select suitable sets of filter parameters primarily for SNR=5 dB. The result of employing the proposed filter is shown in Figure 4.c. In the proposed approach, the parameters of the NPSO method, as for other evolutionary algorithms, are manually chosen as follows: population size=30; C_1=C_2=2; dimension=2; iteration=50; w=1; $2 \le K \le 10$; $3 \le N \le 201$. It must be noted, however, that the performance of the NPSO is robust to small deviations from this set of parameters. Finally, note that in this filter, K must be less than N and N must be odd.

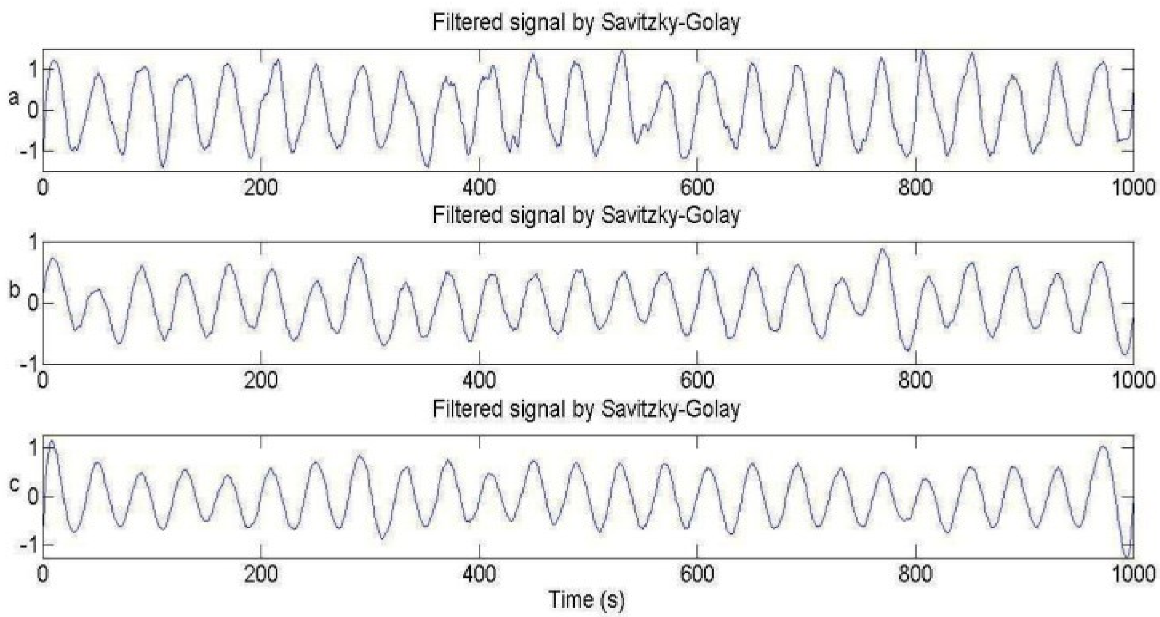

Figure 3. Results of applying three different sets of K and N for the Savitzky-Golay filter; (a) K=3 and N=19, (b) K=5 and N=31, and (c) K=3 and N=61.

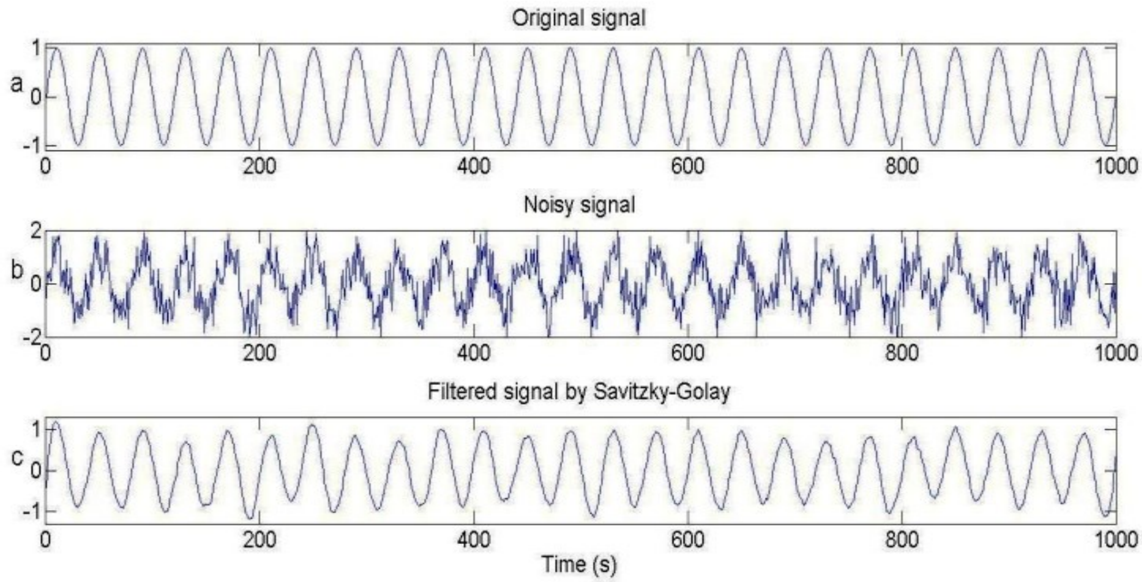

Figure 4. Improved Savitzky-Golay filter by NPSO; (a) original signal, (b) noisy signal (SNR=5 dB), and (c) optimal filtered signal.

2.1.2. Ensemble Empirical Mode Decomposition

The use of EMD has been proved to have many advantages in biomedical signal processing [13]. However, EMD results may suffer from 1) Mode mixing, whereby either an IMF includes different oscillatory modes, or one mode is in different IMFs; and 2) Aliasing when there are overlapping of IMF spectra caused by a sub-Nyquist nature of extrema sampling [7]. Hence, in this paper we propose to employ EEMD, instead of EMD, to reduce the noise.

The EEMD algorithm is explained briefly as follows:

1) A white noise signal, $n(t)$, is added to the signal $x(t)$:

$x_i(t) = x(t) + n_i(t)$, $i \in [1, N]$, with N suggested to be a few hundreds.

2) EMD is performed on each $x_i(t)$.

3) The ensemble mean of each IMF is taken as the final result [21].

As stated in [1], the residual signal obtained by EEMD can be considered as a filtered version of the signal extracted from an original signal combined with some noise sources with mean values of zero. In Figure 5, we can see the result of decomposition performed by EEMD of the filtered test signal. This figure illustrates that modes are ordered from highest to lowest frequencies. As mentioned before, the very important advantage of employing EEMD is that unlike more traditional filtering techniques, the EEMD parameters do not need to be adjusted.

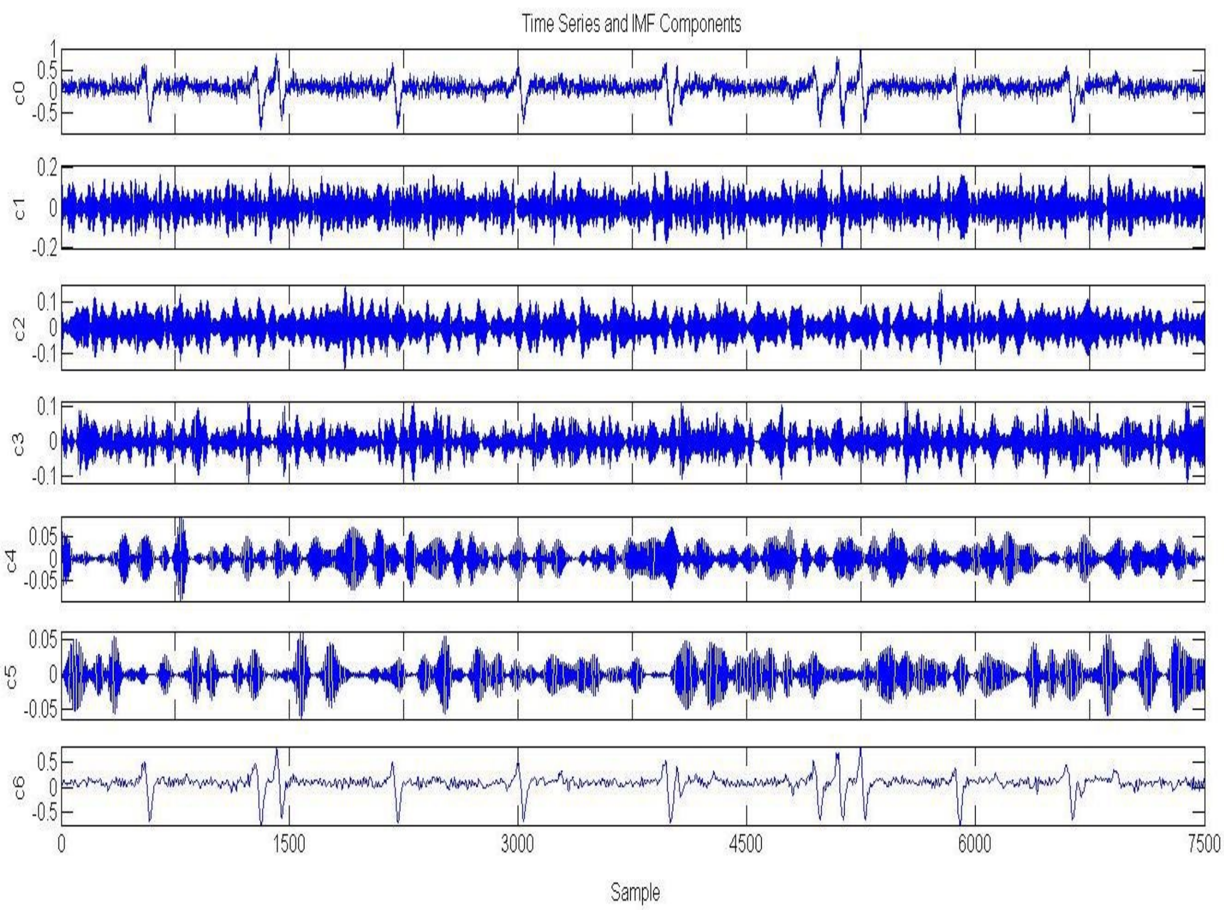

Figure 5. Components of the restored realistic synthetic signal by EEMD. The first time series is the filtered signal. The decomposition yields 5 IMF and a residual. The IMFs are the time-frequency constituents or components of the realistic synthetic neuronal signal.

2.2. Hilbert transform

After applying the noise reduction algorithms and to increase the accuracy of the spike detection methods, we propose to employ the Hilbert transform to enhance the spikes [22]. Consider the concept of the analytic signal (also named pre-envelope) of a signal $x(t)$. This can be expressed by:

$$y(t) = x(t) + j\hat{x}(t) \tag{2}$$

The envelope $B(t)$ of $y(t)$ can be defined as:

$$B(t) = \sqrt{x^2(t) + \hat{x}^2(t)} \tag{3}$$

One of the most important characteristics of the Hilbert transform is that it is an odd function. In other words, it will cross zero on the x-axis every time that there is an inflexion point in the original waveform. Correspondingly, a crossing of the zero between consecutive positive and negative inflexion points in the original waveform will be demonstrated as a spike in its Hilbert transformed conjugate. This can be seen in Figure 6. This remarkable characteristic can be used to develop an elegant and much easier way to find the spike of a signal [14, 22].

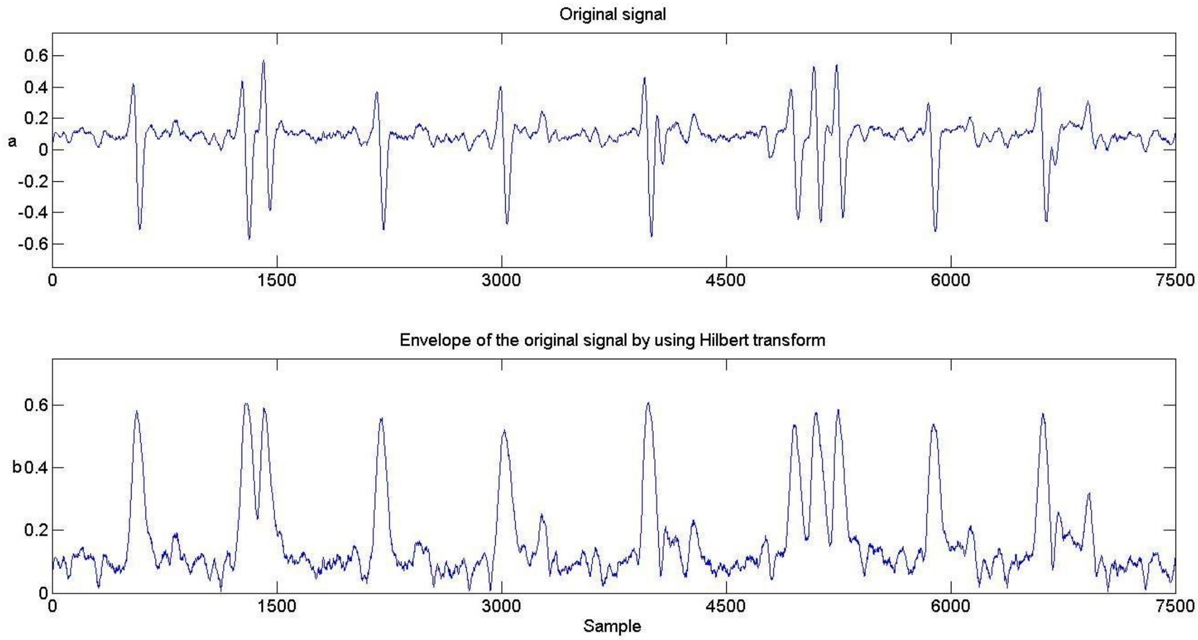

Figure 6. The original signal (a) and the signal after the proposed Hilbert transform was applied (b).

2.3. Two hybrid approaches for spike detection

After using Hilbert transform, the literature describes some methods to detect the spikes. They are based on SNEO, KF, standard deviation, and matching algorithms. Each of them has its advantages and disadvantages. We propose two techniques to combine some of the conventional methods. These proposed techniques are based on the fuzzy and probability concepts to increase the accuracy of spike detection approaches. For each sample, we consider:

$$HC = \frac{\lambda_1 SDA_1 + \lambda_2 SDA_2 + \ldots + \lambda_n SDA_n}{SDA_1 + SDA_2 + \ldots + SDA_n} \tag{4}$$

where if the spike of the ith spike detection method is detected $\lambda_i = 1$ else $\lambda_i = 0$. n is the number of considered spike detection methods and SDA_i is spike detection accuracy of ith considered method by using semi-real data. In fact, this technique is originated from the concept of existence or absence probability of a sample as a spike. Thus, if this probability is more than 0.5 we assume this signal sample is indeed a spike and vice versa. As it is clear, for semi-real data if SDA_m is larger than SDA_n, mth method is more reliable and trustworthy than nth method, so we show this effect on Equation (5).

Two different parameters, namely, the true positive (TP) and false positive (FP) ratios were used to evaluate the performance of the proposed and conventional methods. These parameters are defined as $TP = \left(N_t / N \right)$, and $FP = \left(N_f / N \right)$; where N_t, and N_f respectively represent the number of correctly and falsely detected spikes and N shows the actual number of spikes. It should be mentioned, since the false negative (FN) parameter used to assess the spike detection methods is dependent on TP (TP=1-FN), in this paper we only consider TP and FP ratios.

Considering that FP is based on the inability to detect spikes, we define $SDA = \left(\frac{TP + (1 - FP)}{2} \right)$. It is worth noting that TP ratio is known as sensitivity too [23].

As an example, we consider a part of a real signal of the CARMEN project managed by Prof. Leslie S. Smith [24]. This part of the signal is shown in Figure 7.a. Some spike detection approaches for semi-real neuronal data were presented in [1]. We now combine five of these methods to assess the real neuronal signal. Based on the SDAs of those methods provided in Table 1 in [1] and on the fact that the real signal has about SNR equals to 0dB, by replacing TP

and FP values in the above equation we have $SDA1$=0.9, $SDA2$ = 0.87, $SDA3$ = 0.83, $SDA4$ = 0.89, and $SDA5$ = 0.86.

Hence, for the first line we have $HC(1) = \dfrac{0*0.9 + 1*0.87 + 0*0.83 + 0*0.89 + 0*0.86}{0.9 + 0.87 + 0.83 + 0.89 + 0.86} < 0.5$.

Thus, the sample of the first line cannot be considered as a spike. Considering $HC(2)$, $HC(4)$, $HC(5)$, $HC(6)$, or $HC(8)$ is less than 0.5, 2^{nd}, 4^{th}, 5^{th}, 6^{th}, or 8^{th} lines are not a spike. Also, since $HC(3)$, $HC(7)$, or $HC(9) \geq 0.5$, 3^{rd}, 7^{th}, or 9^{th} lines can be considered as spikes.

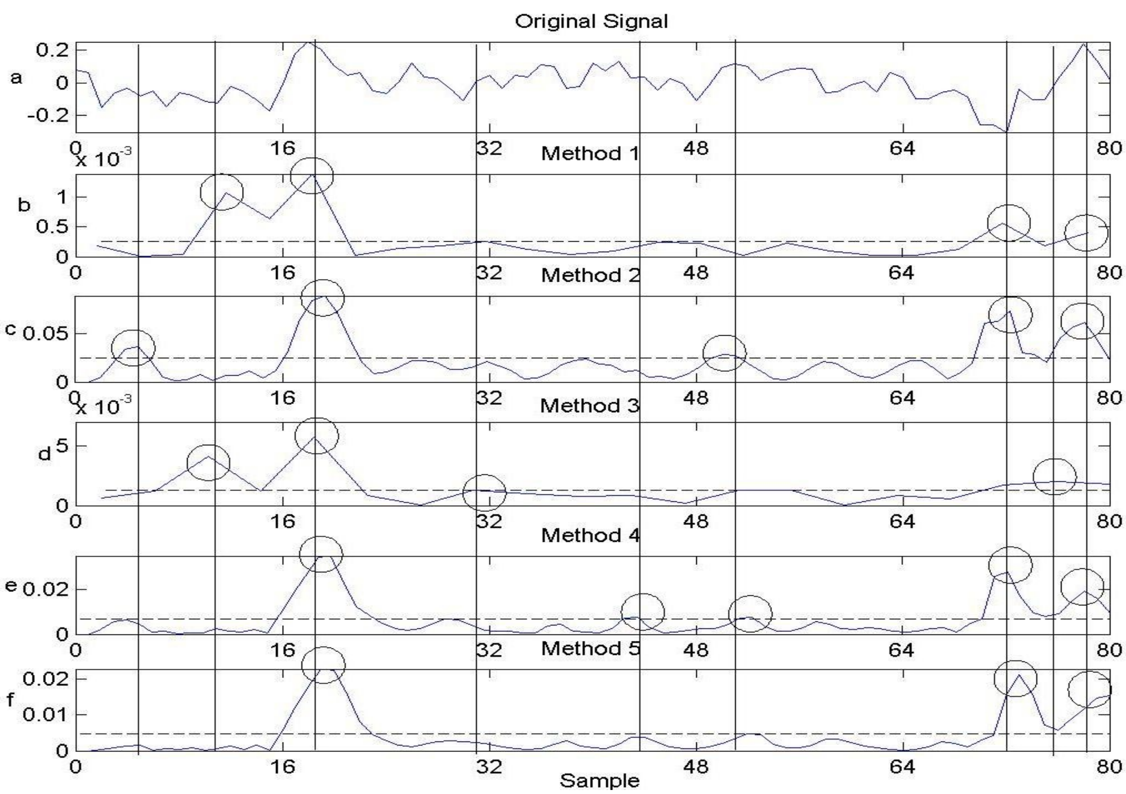

Figure 7. The proposed method for combination four existing methods; (a) original signal, (b) FD with DWT, (c) FD with Savitzky-Golay, (d) SNEO with DWT, (e) standard deviation with DWT, and (f) SNEO with Savitzky-Golay filter.

Usually, when a window moves along the signal, there are some peaks higher than a defined threshold named spikes. It is obvious that the amplitudes of the spikes are not alike. As can be seen in Figure 7.d, each of the four potential spikes detected by the method 3 has different amplitude. There is little room for doubt that we should consider each of them separately. To be more precise, the effect of the 2nd potential spike is much more pronounced than for the 3rd or 4th spike.

We also have another proposal to combine some existing methods based on the fuzzy and probability theory. In this method, we consider each answer as a fuzzy number between 0 and 1. Assume Figure 8 is an output of using a window-based spike detection approach. There is no doubt that for the first peak and the third peak attained by a window-based spike detection method, the probabilities of being the real spikes are 1 and 0.5 respectively.

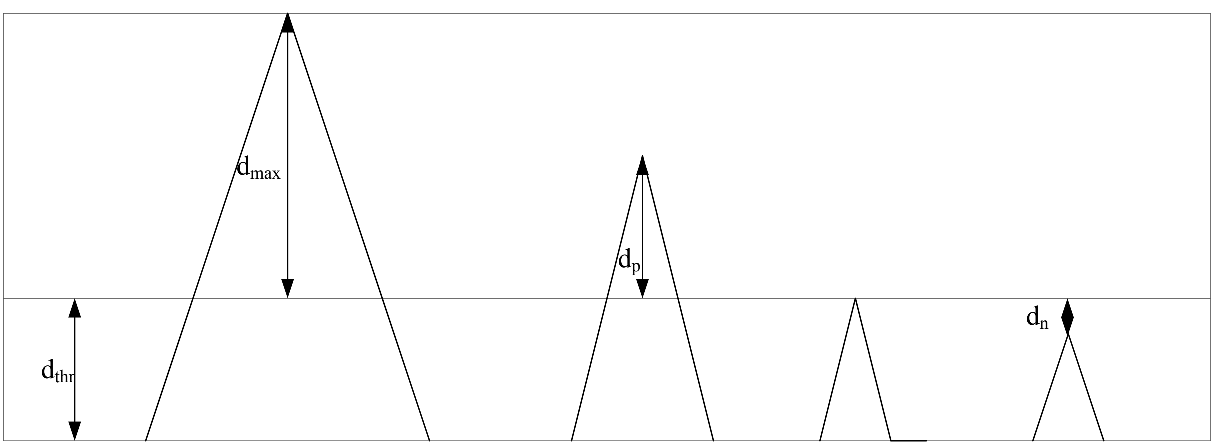

Figure 8. The output when a window-based spike detection approach is employed.

To generalize the concept, we can define two functions as follows:

$$h_{d_p} = 0.5 + \frac{d_p}{2d_{\max}} \tag{5}$$

$$h_{d_n} = 0.5 - \frac{d_n}{2d_{thr}} \tag{6}$$

where d_p and d_n are the distance between a defined threshold and a peak upper and under of the threshold respectively and h_{d_p} and h_{d_n} respectively are the fuzzy amount for a peak upper and lower than a defined threshold. It is worth noting that when d_p=d_{max}, then $h_{d_p} = 1$ as well as if the amplitude of a peak equals with the defined threshold or d_p=0, then $h_{d_p} = 0.5$.

Using the definition, unlike employing the conventional methods which have 0 and 1 for each peak, we can define much more precise amounts based on the fuzzy theory as follows:

$$HCF = \frac{\lambda_1 SDA_1.h_{d_1} + \lambda_2 SDA_2 h_{d_2} + ... + \lambda_n SDA_n.h_{d_n}}{SDA_1 + SDA_2 + ... + SDA_n} \tag{7}$$

where h_{d_i} is $h_{d_{Pi}}$ or $h_{d_{ni}}$ when the peak is respectively higher or lower than the defined threshold. It should be mentioned that this kind of definition is very valuable for combination of a number of spike detection methods. For example, for the second line of Figure 7, we have:

$$HCF(2) = \frac{1*0.9*(0.5+\frac{0.7}{0.9}) + 0*0.87*0 + 1*0.83*(0.5+\frac{0.45}{0.9}) + 0*0.89*0 + 0*0.86*0}{0.9+0.87+0.83+0.89+0.86} < 0.5$$

thus, the sample of the second line cannot be considered as a spike. Like the results of the first method for combination of spike detection approaches, because $HCF(1)$ $HCF(2)$, $HCF(4)$, $HCF(5)$, $HCF(6)$, and $HCF(8)$ are less than 0.5, each of 1st, 2nd, 4th, 5th, 6th, and 8th lines is considered not a spike. However, since $HC(3)$, $HC(7)$, or $HC(9) \geq 0.5$, 3rd, 7th, or 9^{th} line can be considered a spike. The flow chart of the proposed Approach to do spike detection is illustrated in Figure 9.

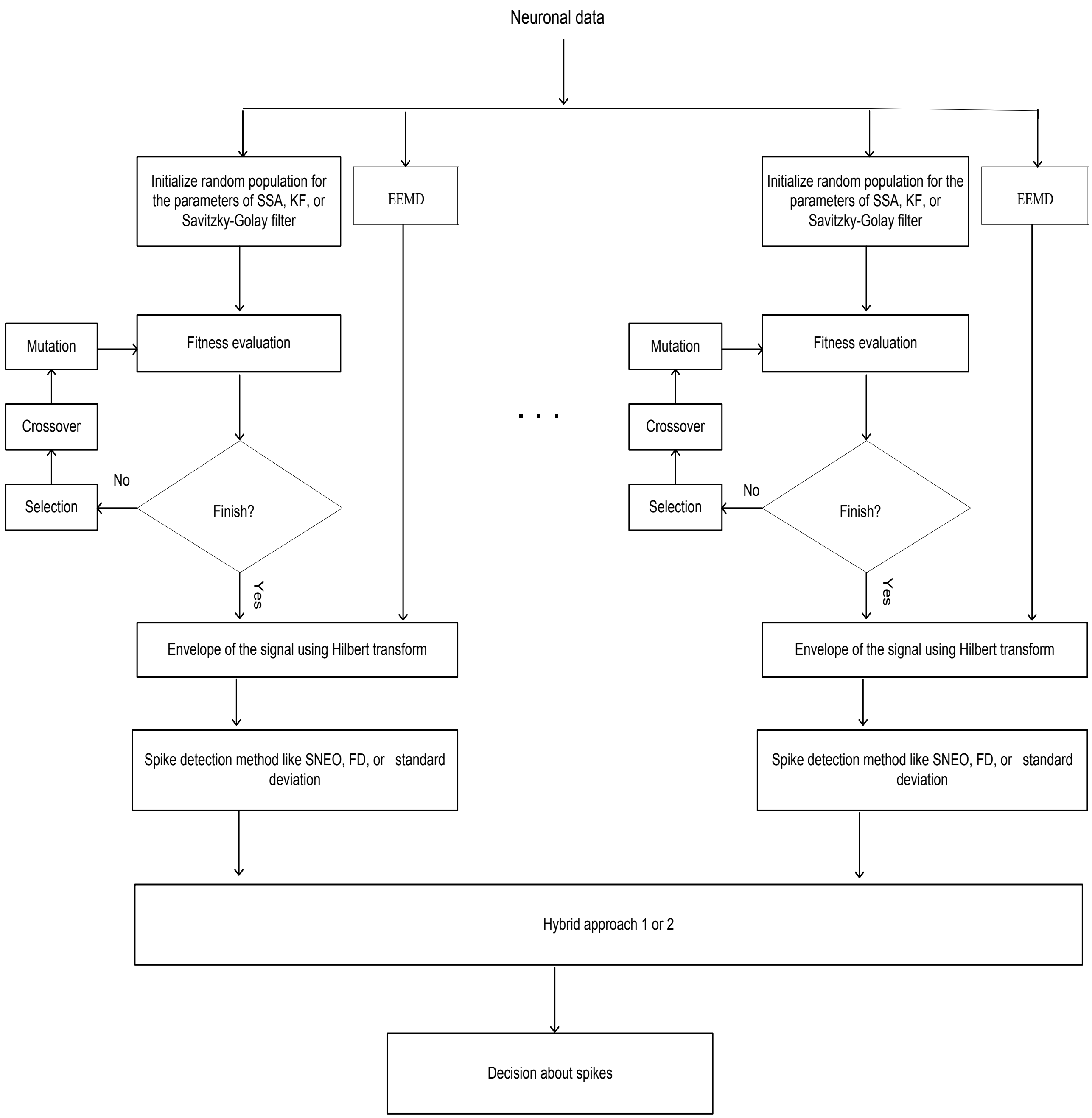

Figure 9. Flowchart of the proposed approach

3. Simulation Data

3. 1. Realistic Synthetic Neuronal Signals

Because of the lack of ground-truth data (i.e., spike timings for each neuron) spike detection methods are often difficult to evaluate. In [25], the generation and transmission of intracellular signals from neurons to an extracellular electrode have been modeled and a set of MATLAB functions based on this have been provided. The codes have been used here to generate a set of realistic synthetic neural data. They produce realistic signals from a set of nearby neurons including interference from more distant neurons and Gaussian noise. These data best resemble the output of deep mesio-temporal brain discharges observed at cortical electrodes. The model also includes correlated and uncorrelated spike noises in neuronal data as well as some Gaussian noise, to imitate the effect of thermal and amplifier noise [25].

By following this synthesizing method, we have randomly generated 70 realistic synthetic neuronal data each including Gaussian noise with SNR=-5, 0, 5, 10, 20 and 50 dBs. For each SNR level, each data contains 12 to 14 spikes. Therefore, we have about 70*6*13=5460 spikes to test. One of 70 signals that contains 13 spikes with SNR=5 dB, randomly selected, shown in Figure 5.C.

3. 2. Real Neuronal Signal

In addition to a set of realistic synthetic neural data, we evaluated the proposed and existing approaches for the real neuronal signals. The data is a part of a real signal of the CARMEN project managed by Prof. Leslie S. Smith [24]. It is approximately 900 seconds long and 20,000 Hz.

4. Simulation Results

Three different parameters, including the true positive (TP) miss or false negative (FN) and false positive (FP) ratios were used to evaluate the performance and effectiveness of the proposed methods. TP and FP were introduced in Section 2 and $\mathrm{FN} = \left(N_m / N \right)$, where N_m shows the number of missed detected spikes.

In Table 1, all of the spike detection approaches, which have been proposed in [1], improved by Hilbert transform and intelligent filter for the semi-real data are shown. In addition, we replace the EMD with EEMD. By comparison between the results in this table and Table 1 in [1], it can be observed that the majority of results are slightly increased by about 1% to 3%in comparison with Table 1 in [1].

Table 1: Results of these suggested, improved, and existing methods on the realistic synthetic neuronal data

Method	Parameters	-5 dB	0 dB	5 dB	10 dB	20 dB	50 dB
SNEO [1]	TP	40%	48%	64%	84%	98%	100%
	FN	60%	52%	46%	16%	2%	0%
Improved SNEO by DWT and Hilbert transform	TP	96%	97%	100%	100%	100%	100%
	FN	4%	3%	0%	0%	0%	0%
	FP	47%	30%	0%	0%	0%	0%
Improved SNEO by intelligent SSA, Savitzky-Golay filter and Hilbert transform	TP	95%	97%	100%	100%	100%	100%
	FN	5%	3%	0%	0%	0%	0%
	FP	51%	22%	2%	0%	0%	0%
Improved SNEO by intelligent SSA and Hilbert transform	TP	**100%**	**100%**	100%	100%	100%	100%
	FN	**0%**	**0%**	0%	0%	0%	0%
	FP	**25%**	**8%**	2%	0%	0%	0%
Improved SNEO by EEMD and Hilbert transform	TP	80%	91%	**100%**	**100%**	**100%**	**100%**
	FN	20%	9%	**0%**	**0%**	**0%**	**0%**
	FP	78%	39%	**0%**	**0%**	**0%**	**0%**
Improved SNEO by intelligent KF and Hilbert transform	TP	97%	98%	99%	100%	100%	100%
	FN	3%	2%	1%	0%	0%	0%
	FP	53%	19%	2%	0%	0%	0%
Spike detection using FD, DWT, and Hilbert transform	TP	96%	98%	100%	100%	100%	100%
	FN	4%	2%	2%	0%	0%	0%
	FP	46%	18%	2%	0%	0%	0%

Spike detection using FD, intelligent Savitzky-Golay filter and Hilbert transform	TP	97%	99%	100%	100%	100%	100%
	FN	3%	1%	0%	0%	0%	0%
	FP	69%	40%	39%	25%	32%	25%
Spike detection using FD, intelligent SSA, and Hilbert transform	TP	98%	99%	98%	100%	100%	100%
	FN	2%	1%	2%	0%	0%	0%
	FP	10%	16%	6%	10%	4%	2%
Spike detection using FD, EEMD and Hilbert transform	TP	84%	90%	100%	100%	100%	100%
	FN	16%	10%	0%	0%	0%	0%
	FP	84%	54%	12%	10%	4%	4%
Spike detection using FD, intelligent KF and Hilbert transform	TP	96%	98%	100%	100%	100%	100%
	FN	4%	2%	0%	0%	0%	0%
	FP	61%	41%	41%	30%	25%	22%
Spike detection using standard deviation, DWT, and Hilbert transform	TP	100%	100%	100%	100%	100%	100%
	FN	0%	0%	0%	0%	0%	0%
	FP	40%	20%	10%	14%	15%	11%
Spike detection using standard deviation, intelligent Savitzky-Golay filter, and Hilbert transform	TP	98%	96%	100%	100%	100%	100%
	FN	2%	4%	0%	0%	0%	0%
	FP	64%	26%	30%	13%	18%	16%
Spike detection using standard deviation, intelligent SSA, and Hilbert transform	TP	98%	98%	100%	100%	100%	100%
	FN	2%	2%	0%	0%	0%	0%
	FP	50%	20%	16%	10%	14%	10%
Spike detection using standard deviation EEMD, and Hilbert transform	TP	83%	90%	100%	100%	100%	100%
	FN	17%	10%	0%	0%	0%	0%
	FP	78%	44%	18%	14%	13%	8%
Spike detection using standard deviation, intelligent KF and Hilbert transform	TP	97%	98%	98%	100%	100%	100%
	FN	3%	2%	2%	0%	0%	0%
	FP	61%	24%	25%	16%	17%	14%
NCED [12]	TP	96%	94%	96%	98%	98%	98%
	FN	4%	6%	4%	2%	2%	2%
	FP	62%	54%	42%	28%	22%	16%
The first proposed combination method	TP	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**
	FN	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**
	FP	**6%**	**5%**	**1%**	**0%**	**0%**	**0%**
The second proposed combination method	TP	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**
	FN	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**
	FP	**6%**	**4%**	**0%**	**0%**	**0%**	**0%**

As can be seen in Table 1, the performance of KF is similar to Savitzky-Goaly filter. The results demonstrate that DWT has better performance than Savitzky-Golay filter and both of them can achieve considerably better spike detection than SNEO. As can be observed in Table 1, when

SNRs>0, improved SNEO by EEMD and Hilbert transform performs best in terms of all the parameters. In contrast, when SNRs<0, SNEO with Hilbert transform and intelligent SSA is the best approach with regard to TPs and FNs not only among SNEO-based methods but also among all the proposed methods. The best method using standard deviation regarding to TPs and FNs is achieved using DWT.

Moreover, the final rows of the table contain NCED as the best algorithm in [12], and the proposed hybrid approaches. As it can be observed, the two combination approaches enhance the existing accuracies largely, with the second hybrid approach is slightly better than the first one.

After assessing the proposed and conventional methods on realistic synthetic neural data, these methods were evaluated using real neuronal signals. In Table 2 the two best algorithms proposed in [1], namely improved SNEO by SSA and spike detection using FD and SSA, NCED (the best algorithm proposed in [12]) and the two proposed hybrid approaches in this study are compared using the real neuronal data. Like the realistic synthetic neuronal data, for the real neuronal data, the two hybrid approaches are superior with regard to all the three parameters TP, FN and FP to the aforementioned existing methods, even though the second hybrid algorithm performs slightly better than the first one. These methods are superior to NCED as the best method among various approaches suggested in [12].

Table 2. Comparison of spike detection rates for two best proposed methods, the proposed combination approaches, the two best algorithm proposed in [1] and NCED method [12] as one of the best spike detection mehods tesed in real neuronal data.

Method	TP	FN	FP
Spike detection using FD and SSA [1]	94%	6%	17%
Spike detection using FD and SSA method [1]	91%	9%	12%
NCED [12]	89%	11%	21%

The first proposed combination method	97%	3%	8%
The second proposed combination method	97%	3%	7%

5. Conclusions

The aim of the piece of research is to investigate and illustrate the capability of the intelligent filtering approaches, and two novel hybrids ensemble methods to detect the extracellular neuronal data. In many of conventional noise reduction algorithms, such as SSA, there are several parameters that must be adjusted using many trials. We have proposed using an intelligent approach to adjust the SSA and KF, and employing the residual signal obtained by EEMD. It is worth mentioning that the novel intelligent filter reduces the effect of noise and it can be used in many other applications. In addition, we took the Hilbert transform of the neuronal data to turn the negative spikes into positive ones and, consequently, increase the accuracy of almost every existing spike detector. Finally, in order to boost the performance of the conventional approaches, we have proposed two novel and influential techniques based on combination of the conventional spike detection methods. The results indicate superiority of the proposed methodology.

Future research works will seek to improve our methods by using a number of approaches based on data fusion, combination or ensemble concepts used in classification and clustering to combine some existing spike detection methods. Spike sorting can also be considered as another step to follow after spike detection in the future.

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